Analyzing Indirect Treatment Comparisons in EUnetHTA Assessments: Lessons Learned for the Implementation of EU Joint Clinical Assessments?

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Key Takeaway

The observed low acceptance of ITC methods, coupled with perceived limitations regarding the evidence base from previous EUnetHTA REAs, serves as an indicator for some of the potential future challenges for EU JCA:

- Research questions related to multiple treatment comparators requiring indirect comparisons
- Supporting JCA assessors and national HTAs in the evaluation and interpretation of ITCs to enable decision-making

Conclusions

The EUnetHTA REA review confirms that multiple analyses and ITCs were necessary to address multiple PICOs, which considerably increased evidentiary requirements.

Although more than half (52%; 12/23) of all submitted REAs required ITCs to generate comparative evidence, the ITC data and/or methods were deemed appropriate by the EUnetHTA assessors in only one (4%) of the submitted ITCs, despite HTD rationale.

References

1. European Union. Regulation (EU) 2021/2282. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32021R2282
2. European Commission. Health technology assessment - joint clinical assessments of medicinal products. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13708-Health-technology-assessment-joint-clinical-assessments-of-medicinal-products_en.
3. Macabeo B, Rotrou T, Millier A, François C, Laramée P. The Acceptance of Indirect Treatment Comparison Methods in Oncology by Health Technology Assessment Agencies in England, France, Germany, Italy, and Spain. Pharmacoecon Open. 2024 Jan;8(1):5-18
4. European Network of Health Technology Assessment(EUnetHTA).EUnetHTA JA 1-2 Assessment reports - Relative Effectiveness Assessment (REA) of Pharmaceuticals. https://www.eunethta.eu/assessment-archive-2006-2015/
5. European Network of Health Technology Assessment (EUnetHTA). EUnetHTA JA3 Assessment reports - Assessments REA (2016 - 2021). https://www.eunethta.eu/rapid-reas/

Disclosures

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Introduction

- The European Regulation 2021/2282[1] on Health Technology Assessment (HTA) will be applied as of January 12, 2025, mandating the evaluation of relative clinical effectiveness for new active substances through European Union (EU) Joint Clinical Assessments (JCA).
- Head-to-head treatment comparisons are often unavailable versus all treatment options; indirect treatment comparisons (ITC) become indispensable in meeting the numerous population, intervention, comparators, and outcomes (PICO) criteria to support decision-making.
- However, uncertainties persist regarding evaluating various ITC methods in addressing the numerous PICO criteria and data availability.
- This study aimed to understand ITC acceptability by analyzing ITC-specific data from pilot European Network for HTA (EUnetHTA) relative effectiveness assessments (REA) conducted between 2006 and 2021, providing valuable insights into their potential implications for future JCAs.

Methods

- All 23 EUnetHTA REAs across Joint Actions 1 to 3 for pharmaceutical products were assessed.
- Information related to the PICO, ITC methods, ITC limitations and critiques, and relative effectiveness conclusions were systematically extracted to identify critical information and trends based on indirect evidence gathered.
- Assessments of ITCs by EUnetHTA were categorized into acceptance and limitations categories, adapted from Macabeo et al., 2024[3] (Figure 1).
- The referencing of EUnetHTA REAs in national HTAs was also investigated for the National Institute of Health and Care Excellence, Haute Autorité de Santé, Gemeinsamer Bundesausschuss, Zorginstituut Nederland, and Tandvårds- och läkemedelsförmånsverket.

Figure 1: Categorization of EUnetHTA's assessment of ITCs

Appropriate	Unsuitable	Unclear
ITC acceptance categories		
• Clearly stated that ITC was appropriate or adequate	• Clearly stated that ITC was not appropriate or adequate	• 3a. Should be interpreted with caution • 3b. No firm conclusions • 3c. Results are not reliable
ITC limitations issued by EUnetHTA assessors		

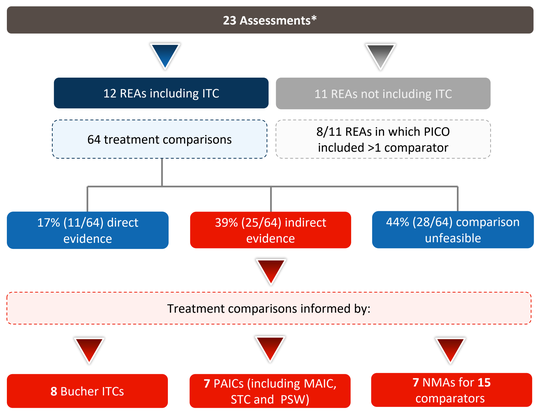
• **Related to data (1):**
  • 1a) Heterogeneity (trials or populations; interventions/comparators; outcomes)
  • 1b) Sample size
  • 1c) Related to subgroup data
  • 1d) Scarcity of data
  • 1e) Limitations related to effect modifiers and prognostics variables
• **Related to methodology (2):** Feasibility of ITCs; statistical methods
• **Related to uncertainty (3):** Missing sensitivity analyses; predictive vs. real-world data
• **Other (4):** Limitations not specified; submission considered incomplete		

Adapted from Macabeo et al., 2024[3]
Abbreviations: EUnetHTA, European Network for Health Technology Assessment ; ITC, indirect treatment comparison

Results

- EUnetHTA conducted 23 REAs of pharmaceutical products between 2006 and 2021; nine were in oncology indications, and 14 were in non-oncology indications.
  - Twelve REAs (52%) included at least one ITC (Table 1), with a median of four comparators per REA (range 1–18), with a total of 64 comparisons across all REAs.
  - Direct evidence covered 17% (11/64) of the required comparisons, while 39% (25/64) relied on indirect evidence. Neither direct nor indirect comparisons were feasible in 44% (28/64) of the REAs (Figure 2).
  - Eight Bucher ITCs, seven population-adjusted indirect comparisons (PAIC), and seven network meta-analyses (NMA; for 15 comparators) were used.
    - Five treatment comparisons were informed by two ITC methods.

Figure 2: Summary of ITC evidence in EUnetHTA REAs



*Five comparators were informed by two ITC methods. For PJTA08, three ITC methods were submitted, but only two methods were considered in the assessment by the EUnetHTA reviewers.
Abbreviations: ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; PICO, population, intervention, comparators, and outcomes; PSW, propensity score weighting; REA, relative effectiveness assessment; STC, simulated treatment comparison

Results (cont.)

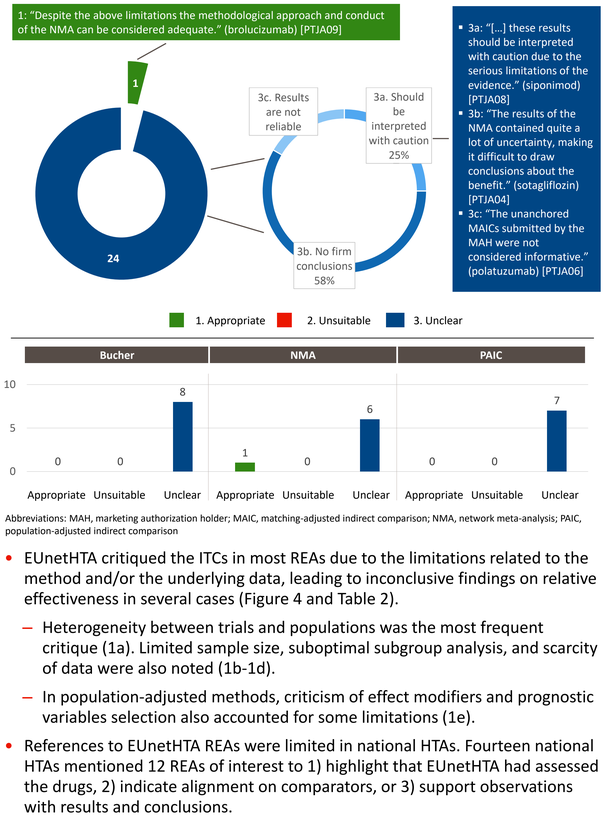
- The acceptance of ITCs was categorized as unclear in all but one of the 25 comparisons (96%) (Figure 3).
- One ITC (an NMA) was classified as appropriate, and none were deemed unsuitable.
  - Although the acceptance level of submitted ITCs was unclear in many assessments, the ITC results were still included in the final assessment report. Whether the critiques and concerns raised were significant enough to omit the results was uncertain.

Table 1: Overview of EUnetHTA REAs[4,5]

Code	Joint action	Year	ATMP/ oncology	Technology	Condition	Comp	REA based on		REA not feasible
							Direct evidence	Indirect evidence	
REAs with an ITC									
PTJA16	JA3	2021	Yes	Venetoclax	Acute myeloid leukemia	5	1	1	3
PTJA12	JA3	2020	Yes	Glasdegib	Acute myeloid leukemia	4	1	2	1
PTJA11	JA3	2020	No	Cefiderocol	Aerobic gram-negative bacterial infections	1	0	1	0
PTJA09	JA3	2020	No	Brolucizumab	Neovascular macular degeneration	3	1	1	1
PTJA08	JA3	2020	No	Siponimod	Secondary progressive multiple sclerosis	7	0	1	6
PTJA07	JA3	2019	No	Ustekinumab	Ulcerative colitis	5	0	5	0
PTJA06	JA3	2020	Yes	Polatuzumab vedotin	Diffuse large B-cell lymphoma	8	0	3	5
PTJA04	JA3	2019	No	Sotagliflozin	Diabetes mellitus	4	1	2	1
PTJA03	JA3	2018	Yes	Alectinib	ALK+ advanced non-small cell lung cancer	2	1	1	0
PTJA01	JA3	2017	Yes	Midostaurin	Acute myeloid leukemia	3	2	1	0
NR	JA1-2	2014	No	Canagliflozin	Diabetes mellitus	18	4	4	10
WP5-SA4	JA1-2	2015	Yes	Ramucirumab	Gastric/gastro-esophageal carcinoma	4	1	3	0
REAs with no ITC									
PTJA17	JA3	2021	Yes	Elivaldogene autotemcel	Cerebral adrenoleukodystrophy	Excluded from review*			
PTJA14	JA3	2020	No	Pretomanid	Tuberculosis	Excluded from review*			
PTJA13	JA3	2019	No	Satralizumab	Neuromyelitis optica spectrum disorders	Excluded from review*			
PTJA10	JA3	2020	No	Crizanlizumab	Sickle cell disease	Excluded from review*			
PTJA05	JA3	2020	Yes	Enasidenib	Acute myeloid leukemia	Excluded from review*			
PTJA02	JA3	2017	Yes	Regorafenib	Hepatocellular carcinoma	Excluded from review*			
CoreHTA2	JA1-2	2015	No	Immunoglobulins	Alzheimer	Excluded from review*			
WP5-SA3	JA1-2	2015	Yes	Sorafenib	Thyroid carcinoma	Excluded from review*			
WP5-SA6	JA1-2	2015	No	9 direct-acting antivirals	Hepatitis C	Excluded from review*			
WP5-SA5	JA1-2	2015	No	Vorapaxar	Myocardial infection	Excluded from review			
WP5-SA1	JA1-2	2013	No	Zostavax	Prevention of herpes zoster	Excluded from review			

* EUnetHTA REAs excluded from review due to absence of ITC in final assessment report
Abbreviations: ALK, anaplastic lymphoma kinase; ATMP, advanced therapy medicinal product; comp, comparator; NR, not reported; REA, relative effectiveness assessment

Figure 3: ITC evidence in REAs by acceptability categorization

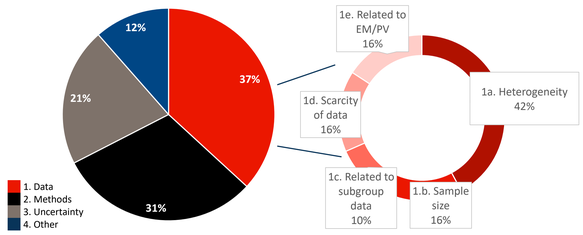


Abbreviations: MAH, marketing authorization holder; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison

- EUnetHTA critiqued the ITCs in most REAs due to the limitations related to the method and/or the underlying data, leading to inconclusive findings on relative effectiveness in several cases (Figure 4 and Table 2).
  - Heterogeneity between trials and populations was the most frequent critique (1a). Limited sample size, suboptimal subgroup analysis, and scarcity of data were also noted (1b-1d).
  - In population-adjusted methods, criticism of effect modifiers and prognostic variables selection also accounted for some limitations (1e).
- References to EUnetHTA REAs were limited in national HTAs. Fourteen national HTAs mentioned 12 REAs of interest to 1) highlight that EUnetHTA had assessed the drugs, 2) indicate alignment on comparators, or 3) support observations with results and conclusions.
  - The impact of the REAs on the HTA or national decision-making was unclear.

Results (cont.)

Figure 4: Overview of ITC limitations



- 1a: "The studies used show heterogeneity of the study population characteristics such as performance status, background medication and outcome evaluation, and some differences in secondary outcomes." (ramucirumab) [WP5-SA4]
- 1b: "[…] it was an open-label, descriptive study of limited size, so can only be regarded as supportive of efficacy." (cefiderocol) [PTJA11]
- 1c: "The studies included in the NMA were at high risk of bias for several outcomes and included the mITT populations (also for sotagliflozin), since the BMI subgroup data were unavailable for the comparators." (sotagliflozin) [PTJA04]
- 1d: "The evidence on which all the networks were based was scarce …" (ustekinumab) [PTJA07]
- 1e: "[…] potentially relevant effect modifiers could not be controlled for because of unavailable information from trials included in the ITC." (glasdegib) [PTJA12]

2: "[…] there was a reduction in sample size relative to the ITT population that may not have enough statistical power to detect meaningful differences. This issue is also inherent to MAICs, following the matching and adjustment process." (siponimod) [PTJA08]

3: "[…] because of uncertainties regarding the adequacy of the comparison, this observed result has to be regarded as unsure."(alectinib) [PTJA03]

4: "The assessment of polatuzumab + BR in PICO 1a is incomplete because the MAH did not provide analyses of adverse events for the relevant patient population." (polatuzumab) [PTJA06]

Abbreviations: BMI, body mass index; BR, bendustamine + rituximab; EM, effect modifier; ITC, indirect treatment comparison; MAH, marketing authorization holder; MAIC, matching-adjusted indirect comparison; mITT, modified intent to treat; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; PICO, population, intervention, comparators, and outcomes; PV, prognostic variable

Table 2: Overview of ITC methods, acceptance and limitations per REA

Code	Technology	Comparator	ITC methods				Acceptance	Limitation
			Bucher ITC	PAIC: PSW	PAIC: MAIC/ STC	NMA		
PTJA16	Venetoclax	Low-dose cytarabine	-	✓	-	-	3b. Unclear - No firm conclusions	2. Method 4. Other
PTJA12	Glasdegib	Azacitadine	✓	-	✓	-	3b. Unclear - No firm conclusions	1a, 1b, 1e. Data
		Decitabine	✓	-	✓	-	3b. Unclear - No firm conclusions	1a, 1b, 1e. Data
PTJA11	Cefiderocol	Best available therapy	-	-	-	✓	3c. Unclear - Results are not reliable	1a. Data 3. Uncertainty
PTJA09	Brolucizumab	Ranibizumab	-	-	-	✓	1. Appropriate	2. Method
PTJA08	Siponimod	Interferon-β-1a or -β-1b plus BSC	✓	-	✓	✓*	3a. Unclear - Should be interpreted with caution	1a, 1c. Data 2. Method
PTJA07	Ustekinumab	Adalimumab	-	-	-		3a. Unclear - Should be interpreted with caution	1a, 1d. Data 3. Uncertainty
		Infliximab	-	-	-			1a, 1d. Data 3. Uncertainty
		Golimumab	-	-	-	✓		1a, 1d. Data 3. Uncertainty
		Vedolizumab	-	-	-			1a, 1d. Data 3. Uncertainty
		Tofacitinib	-	-	-			1a, 1d. Data 3. Uncertainty
PTJA06	Polatuzumab vedotin	PICO 1b: Axicabtagene ciloleucel	-	-	✓	-	3c. Unclear - Results are not reliable	1e. Data 2. Method 4. Other
		PICO 1b: Tisagenlecleucel	-	-	✓	-	3c. Unclear - Results are not reliable	1e. Data 2. Method 4. Other
		PICO 1b: Pixantrone	-	-	✓	-	3c. Unclear - Results are not reliable	1e. Data 2. Method 4. Other
PTJA04	Sotagliflozin	Any SGLT2 inhibitor: empagliflozin	-	-	-		3b. Unclear - No firm conclusions	1a, 1c. Data 2. Method 4. Incomplete
		Any SGLT2 inhibitor: dapagliflozin	-	-	-	✓		1a, 1c. Data 2. Method 4. Incomplete
PTJA03	Alectinib	Ceritinib	✓	-	-	✓	3b. Unclear - No firm conclusions	1a, 1e. Data 2. Method 3. Uncertainty
PTJA01	Midostaurin	Induction and consolidation chemotherapy with daunorubicin 90 mg/m2/day during induction	✓	-	-	-	3b. Unclear - No firm conclusions	1a, 1b, 1c, 1d. Data 3. Uncertainty
Not reported	Canagliflozin	Dual therapy: pioglitazone + metformin	-	-	-		3b. Unclear - No firm conclusions	2. Method
		Dual therapy: GLP-1 + metformin	-	-	-	✓		2. Method
		Dual therapy: dapagliflozin + metformin	-	-	-			2. Method
		Triple therapy: GLP1 + metformin + SU	-	-	-			2. Method
WP5-SA4	Ramucirumab	Docetaxel monotherapy	✓	-	-	-	3b. Unclear - No firm conclusions	1a, 1b. Data 2. Method 3. Uncertainty
		Irinotecan monotherapy	✓	-	-	-	3b. Unclear - No firm conclusions	1a, 1b. Data 2. Method 3. Uncertainty
		BSC	✓	-	-	-	3b. Unclear - No firm conclusions	1a, 1b. Data 2. Method 3. Uncertainty

*The NMA was not considered/commented upon by the EUnetHTA reviewers as the results were identical to the Bucher ITC [PJTA08].
Abbreviations: BSC, best supportive care; GLP, glucagon-like peptide; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; PICO, population, intervention, comparators, and outcomes; PSW, propensity score weighting; SGLT2, sodium-glucose transport protein 2 inhibitor; SU, sulfonylurea; STC, simulated trial comparison